REMARKS/ARGUMENTS

Claims 1-13, 16, 17, 21-23, 30, 31, 34 and 36 were pending before this communication. Claims 1-12 are directed to non-elected inventions, and have been canceled in the present amendment. Claims 16 and 23 have been amended to define Applicants' invention with greater particularity. These amendments add no new matter as they are fully supported by the specification and original claims. Applicants reserve the right to pursue non-elected subject matter in a continuing application without prejudice.

Supplemental Information Disclosure Statement

Applicants respectfully inquire as to the status of the Supplemental Information Disclosure Statement filed (mailed on) June 11, 2003. Applicants have not yet received an initialed copy of the form PTO-1449 included therewith as an indication of the cited references as having been considered and made of record. In the event that the original form was lost, a copy of form PTO-1449 as filed is attached herewith.

Withdrawal of Certain Rejections

Applicants acknowledge that the previous rejection of claims 29, 32 and 33, under 35 U.S.C. §112 first paragraph has been withdrawn.

Applicants further acknowledge that the previous rejection of claim 13 under 35 U.S.C. §102(a) as being anticipated by Shan et al. (WO 01/03705) has been withdrawn and that the previous rejection of claims 13 and 16 under 35 U.S.C. §103(a) as being unpatentable over Shan et al. (WO 01/03705) taken with Piper (US 2002/0177602A1) has been withdrawn.

Objections to Claims

Claims 16 and 23 have been objected to because the claim allegedly refers to non-elected additional active agents. Applicants respectfully traverse the rejection, but have amended the claims in order to reduce issues and to expedite the allowance of the present application.

Applicants accordingly request withdrawal of the objection. Applicants reserve the right to pursue non-elected subject matter in a continuing application without prejudice.

Issues under 35 U.S.C. §112 First Paragraph

Claims 13, 16, 17, 21-23, 30, 31, 34 and 36 have been rejected under 35 U.S.C. §112, first paragraph as allegedly not enabled such that a skilled artisan could make and/or use the invention commensurate in scope with the claims. The Examiner alleges (see page 4 of the office action) that while the specification is enabling for a method of treating diabetes type II comprising administering a specific LXR agonist, (compound 1), the specification does not reasonably provide enablement for a method for treating, or reducing the risk of developing or recurrence of diabetes, with the disclosed compound, or treating type II diabetes wherein the structure of the LXR agonist is not defined.

Applicants respectfully traverse the rejection on the grounds that the currently pending claims are fully enabled by the present specification.

Firstly, the application provides an enabling disclosure, and working examples showing *in vivo* animal as well as *in vitro* data that is of direct relevance to the claimed methods of treating, reducing the risk of developing, or recurrence of diabetes with the disclosed LXR agonist. As stated in MPEP 2164.02, an *in vitro* or *in vivo* animal model example in the specification constitutes a working example if that example correlates with a disclosed or claimed *in vivo* use. In this instance, paragraph [0121] and Figure 15 of the instant application, disclose the use of a pan LXR agonist in a mouse model of diabetes, the (*db/db*) mouse, which displays diabetic symptoms such as insulin insensitivity and severe hyperglycemia (elevated blood glucose). The data shows that administration of the pan LXR agonist to the (*db/db*) mouse results in significant reduction in hyperglycemia (Figure 15).

The specification therefore provides *in vitro* and *in vivo* data in a relevant animal model of diabetes development to support the concept that LXR agonists, reduce diet-induced hyperglycemia associated with the development of diabetes. Because a central feature of both the treatment, development and recurrence of diabetes rests upon the control (or lack of control)

of plasma glucose levels, the experimental data presented in the current specification clearly establishes that LXR agonists can enhance glucose metabolism independently of the action of insulin, and therefore have utility for both the treatment, reducing the risk of development, and prevention of recurrence, of diabetes.

Thus in contrast to the Examiners allegations, the Applicants have demonstrated that LXR agonists, by reducing hyperglycemia, are effective in an in vitro model system for the treatment, reduction in the risk of developing, and recurrence of diabetes.

Furthermore, the fact that only one LXR agonist is disclosed in the specification does not necessarily render the specification non-enabled. Applicants respectfully point out that the standard to be applied in establishing a *prima facie* case of non-enablement is set out in part at MPEP 2164.04, including *In re Marzocchi*[1] and the other cases cited therein. With reference to *Marzocchi*, the standard states in part that

> "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the *objective* truth of the statements contained therein which must be relied on for enabling support." (underlining and italics added)

The above standard requires *objective* reasons to doubt the **presumption** of an enabling disclosure. Thus, there must be *objective* reasons why undue experimentation is necessary to make and use the claimed invention. In the present case, the Examiner has not given *objective* reasons why other LXR agonists, all of which would be expected to act on the LXR receptor, would not behave similarly to the LXR agonist disclosed in the specification.

The MPEP 2164.02 states: "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one

[1] 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

skilled in the art (in view of the level of skill and state of the art, and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation." Applicants respectfully submit that **no** *objective* reasons have been provided for why the representative working examples are insufficient to allow one skilled in the art to expect that the genus as claimed is adequately enabled. In the absence of such reasons, the proper conclusion is that one of skill in the art would expect that the genus of LXR agonists would exhibit predictable physiological effects based on their shared ability to activate the LXR nuclear receptor.

In the immediate case here, the Examiner has already acknowledged enablement for the disclosed LXR agonists for treating diabetes based on the *in vitro* data presented. Since other LXR agonists are readily available (for example as disclosed U.S. Patents 5,607,967 and 6,184,215, and PCT publications WO98/32444, WO00/54759, WO00/66611, WO01/03705 and WO01/41704) and would be predicted to act in the same way, i.e. activate LXR and reduce plasma glucose levels, Applicants contend that the claimed methods are also enabled for other members of the claimed genus.

MPEP 2164.02 also states that in order to make a valid rejection, the Examiner should evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claim. Since the Examiner has not stated why one cannot extrapolate the specifically disclosed LXR agonists across the entire scope of the claims covering the genus of LXR agonists, Applicants request that the enablement rejection be withdrawn.

Applicants also respectfully traverse the Examiner's contention that the specification allegedly necessitates undue experimentation. The Examiner presented an undue experimentation analysis based on the eight factors presented in *In re Wands* (858 F2d at 731,737, 8USPQ2d at 1400, 1404 (Fed. Cir. 1988)). Applicants respectfully submit that in addition to the reasons provided above, and as discussed below, the currently pending claims are fully enabled by the present specification, and can be practiced with no more than routine and

repetitive experimentation. Therefore, no undue experimentation is required for the following reasons:

(1) The breadth of claims: The currently pending claims are directed to the use of LXR agonists for the treatment, prevention and occurrence of diabetes, insulin resistance and hyperglycemia.

Based on the instant application, a skilled artisan readily understands that numerous LXR agonists can be readily used in the claimed methods in accordance with the invention as disclosed. No more than routine and repetitive experimentation is needed to use LXR agonists for the treatment, prevention and occurrence of diabetes, insulin resistance and hyperglycemia. Contrary to the position set forth in the Office Action, it is not necessary for the instant application to detail the use of every possible member of the LXR agonist genus to enable the claimed methods.

Additionally because all the claimed methods exploit the demonstrated ability of LXR agonists to reduce plasma glucose levels independently of insulin action, a skilled artisan would expect that all members of this genus would be useful across the entire scope of the claimed methods, i.e. for the treatment, prevention and re-occurrence of diabetes, insulin resistance and hyperglycemia. As discussed below, the specification, state of the art and expectation of similar results demonstrate in sum that the claimed methods could be practiced with any LXR agonist with only routine and repetitive experimentation, such as with optimization of dosing and treatment protocols. Such optimization does not constitute undue experimentation because it is within routine practice and skills in the medical profession. Medical professionals routinely engage in such activities.

In light of the above, Applicants respectfully submit that the breadth of the claims raise no issues in support of the allegation of insufficient enablement.

(2) The absence or presence of working examples: Applicants provide a specific working example of an LXR agonist, and its use in the *db/db* mouse which is a recognized diabetic model system that correlates with various aspects of the development of

diabetes, insulin insensitivity and hyperglycemia in humans. The fact that only one LXR agonist is disclosed in the specification does not necessarily render the specification non-enabled. According to MPEP 2164.04: " ...the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement". The Examiner has not given *objective* reasons why other LXR agonists such as those disclosed for example in WO01/03705, would not behave similarly to the LXR agonist disclosed in the specification when, in fact, it is well known in the art that nuclear receptor ligands for a specific nuclear receptor exhibit similar physiological effects based on the function and activity of the nuclear receptor in question, rather than their chemical structures.

Therefore, the presence and number of working examples does not support the allegation of insufficient enablement.

(3) The state of the prior art and relative skill of those in the art: As pointed out above, representative LXR agonists were known and available at the time the application was filed. Further, the specification provides extensive guidance on how to identify, profile and evaluate potential LXR agonists, for example see paragraphs [0076] and [0049] to [0058] of the present application, by use of no more than routine and repetitive methods.

Diabetes, hyperglycemia and insulin insensitivity are well-established medical conditions and at the time the application was filed it was routine in the art to monitor individuals with diabetes, at risk of developing diabetes, or relapsing into diabetes by measuring blood glucose levels. This knowledge, combined with the instant application's disclosure of the discovery that LXR agonists can reduce hyperglycemia, a skill artisan would immediately recognize that an LXR agonist could be used in the practice of the invention by use of no more than routine testing. For example, measurements of the effect of progressively increasing doses of the LXR agonist on a patient's blood glucose levels can be used to determine optimal conditions for the practice of the claimed invention.

Given the high state of the art, (numerous LXR agonists were known and available) and the relative level of skill in the art, the claimed methods can be readily

practiced without undue experimentation. Accordingly, the state of the prior art and relative skill in the art does not support the allegation of insufficient enablement.

(4) The amount of direction or guidance presented and the quantity of experimentation necessary: Applicants point out that methods of administering drugs for the treatment or prevention of diseases are within the purview of a clinician of ordinary skill in the art, and therefore need not be provided, although general dosage information may be found in paragraphs [0061]-[0075] of the specification.

The MPEP (2164.01(c)) states "For example, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. § 112 first paragraph."

Additionally, Applicants respectfully submit that there is no requirement to provide working examples using various LXR agonists with different structures. This logically follows because there is no objective reason to doubt that an LXR agonist, regardless of diversity in structure, may be used in the claimed methods with no more than routine and/or repetitive testing.

Applicants thus respectfully submit that the amount of direction and guidance is sufficient and no undue amounts of experimentation is necessary to make and use the instant invention.

(5) Predictability or unpredictability of the art: Applicants respectfully point to the experimental data showing the reduction of blood glucose in the diabetic mouse study upon treatment with an LXR agonist, which the Examiner has already acknowledged enablement for the disclosed LXR agonists for treating diabetes based on the in vitro data presented.

As pointed out above, it is well known in the art that nuclear receptor ligands such as the genus of LXR agonists, have predictable characteristics, just as other classes of

nuclear receptor ligands, for example the estrogen receptor (ER) ligands, and peroxisome proliferator-activator receptor (PPAR) ligands exhibit defined, predictable, physiological and pharmaceutical properties that are derived from the biological actions of the nuclear receptor in question. Therefore, and contrary to the allegations in the Office Action, other LXR agonists would be predicted to act in the same way to produce the same results as the example disclosed in the instant application. Stated differently, other LXR agonists would be expected to activate LXR and reduce plasma glucose levels.

MPEP 2164.02 also states that in order to make a valid rejection, the Examiner should evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claim. Since the Examiner has not stated why one cannot extrapolate the specifically disclosed LXR agonists across the entire scope of the claims covering the genus of LXR agonists, contrary to the prevailing art, Applicants contend that the claimed methods are also enabled for other members of the claimed genus. Therefore, Applicants submit that the presence of predictability argues against the alleged insufficiency of enablement.

(6) Nature of the Invention: Applicants were the first to show that the activation of the LXR receptor leads to an increase in the metabolism of glucose thereby reducing hyperglycemia associated with the development of diabetes, insulin sensitivity and in the treatment of diabetes itself in a relevant diabetes model system (see, paragraph [0122] and Figure 15).

Because activation of the LXR receptor would be expected to lead to the same general effects on glucose metabolism, irrespective of the precise chemical structure of the LXR agonist used to activate the receptor, all members of the genus of LXR agonists would be expected to share the same physiological effects in mammalian tissues and would accordingly be useful in the treatment, and prevention of diabetes, insulin resistance and hyperglycemia. Accordingly, and contrary to the allegations in the Office Action, there is no requirement to show the identities and use of all possible LXR agonists in the practice of the instant invention.

Accordingly, it is Applicants' position that based on the teachings of the specification, which the Examiner acknowledges enables practice of the claimed method with the disclosed species, the ordinary skilled artisan would be able to make and use the claimed methods without undue experimentation.

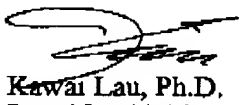
For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of pending claims 13, 16, 17, 21-23, 30, 31, 34 and 36 under 35 U.S.C. §112, first paragraph.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6100 .

Respectfully submitted,



Kawai Lau, Ph.D.
Reg. No. 44,461

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 858-350-6100
Fax: 415-576-0300
Attachments
KL:ps
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